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| 09/972,268 | 10/05/2001 | Peter R. Baum | 3101-A | 4855 |

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| EXAMINER |
|---|
| HADDAD, MAHER M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/972,268 | BAUM ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *59-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/04 has been entered.

2. Claims 59-111 are pending and under consideration.

3. Applicant's IDS, filed 4/01/04, is acknowledged, however, reference No. 1A is crossed out as it is a duplicate of reference 1A filed on the IDS filed 6/30/04. Reference 1B is considered to the extent that it discloses murine nectin-3 polypeptides as stated in Applicant response on page 12 last line and page 13, 1st line.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 60 and 67 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases: "extending from amino acid 58 through the C-terminus of SEQ ID NO:15" claimed in claim 60(c), lines 7-8, and "extending from amino acid 58 through the C-terminus of SEQ ID NO:16" claimed in claim 67(c), lines 7-8, represent a departure from the specification and the claims as originally filed for the same reasons set forth in the previous Office Action mailed 10/03/03.

Applicant's arguments, filed 4/01/04, have been fully considered, but have not been found persuasive.

Applicant argues to the polypeptides of SEQ ID NO 15 and 16 comprise nectin-3 N-terminal amino acid sequences including nectin-3 signal sequences. Applicant asserts that polypeptides of SEQ ID NO: 15 and 16 form which the signal sequence has been removed are described at page 7, lines 5-6 and also at page 52, line 23. Applicant concludes that the specification provides support for polypeptides having N-terminal nectin-3 amino acid sequences from which the

nectin-3 signal sequence has been removed, resulting in such polypeptides having an amino acid sequence extending from amino acid 58 through the C-terminus of the polypeptide.

However, both SEQ ID NO: 15 and 16 contain polyHis tag on the C-terminal, wherein the specification fails to provides support for the amino acid 58 through the C-terminus of either SEQ ID NO:15 or SEQ ID NO:16 which encompass the polyHis tag.

6. Claims 59-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189-250 and 287-342, and SEQ ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration; does not reasonably provide enablement for any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73; any substantially purified polypeptide comprising any amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amion acid identity across the length of amino acids 58-404 of SEQ ID NO:4 or 6 in clai 79, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of amino acids 58 through 404 of SEQ ID NO: 4 or 6 in claim 80; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 86, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95%, or 99% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 87; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12 or 31 in claim 93, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12, or 31 in claim 94; any isolated polypeptide of claim 93 produced by a process comprising (a) culturing a recombinant host cell comprising any "polynucleotide" having nucleotide sequence encoding said polypeptide and (b) isolating said polypeptide in claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising a polynucleotide having a nucleotide sequence encoding said polypeptide or The polypeptide of claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising any polynucleotide having any nucleotide sequence

encoding said polypeptide, wherein said nucleotide sequence is selected from the group consisting of nucleotide4s 172-1026 of SEQ ID NO:3, 5, 9 or 11; nucleotides 172-1212 of SEQ ID NO:3 or 5, and nucleotides 172-1098 of SEQ ID NO: 9 or 11 in claim 102; wherein said polypeptide comprises an amino acid sequence selected from the group consisting of (a) amino acids 58-342 of SEQ ID NO: 4, 6, 10, 12 or 31, (a) amino acids 58-404 of SEQ ID NO:4 or 6, (c) amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, (d) amino acids 74-404 of SEQ ID NO:4 or 6, (e) amino acids 58 through 365 of SEQ ID NO:10, 12, or 31 and (f) amino acids 74-365 of SEQ ID NO:10, 12 or 31 in claim 105, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell into which a polynucleotide comprising a nucleotide sequence encoding said polypeptide has been introduced in claim 111. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed 10/3/03.

Applicant's arguments, filed 4/1/04, have been fully considered, but have not been found persuasive.

Applicant submits that given that the previous Office Action enabled the specification for SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189-250 and 287-342, and SEQ ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration. Applicants state that they cannot find basis for applying this rejection to claims 59-78, such claims being directed to polypeptide sequences that have been shown to possess the nectin-l binding properties referred to (see, for example, Examples 4 through 6 at pages 53-56 of the specification).

However, as stated in the previous Office Action, claims 59-78 recite the term "comprising", which is an open-ended term and expand amino acids 58-404 of SEQ ID NO: 4 or 6; aa 74-365 of SEQ ID NO:10, 12 or 31 or the other fragments of nectin-3 to include additional non disclosed amino acids on either of both sides of the N- and C- terminal of the polypeptide. The specification fails to provide sufficient guidance as to which amino acids outside the core structure of SEQ ID NO: 4 and 6 is essential for maintain its nectin 1 binding activity and which amino acids can be added to the core structure of SEQ ID NO: 4 and 6 and still maintained the same function, besides the full length SEQ ID NO: 2, 4, 6, 8, 10, 12, and 31. The claims fail to meet the enablement requirement for the "how to make" prong of 35 U.S.C. 112, first paragraph: Since the instant fact pattern fails to indicate that a representative number of structurally related compounds is disclosed, the artisan would not know the identity of any non-disclosed compound failing within the scope of the instant claim and consequently would not have known how to make it.

Regarding claims 79-111, Applicant argues that the Office Action notes that a large number of variants would have 80% amino acid identity to amino acid sequences such as amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ ID Nos 4, 6, 10. 12, and 31, and expresses a concern that not all of such variations would be "predictive of

inhibiting endothelial cell migration", thus requiring a level of experimentation that is "excessive and undue". However, this concern does not consider the nature of the experimentation that would be required in using standard techniques such as those disclosed in the application, to make and test such variants for function. It is well established that routine experimentation, even if it must be performed on numerous variants, does not constitute experimentation that is so undue that it cannot be carried out by those of skill in the art. See. for example, Ex parte Mark, 12 U.S.P.Q.Zd (BNA) 1904 (BPAI 1989).

However, in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and use the invention, not how to identify the invention. Until the time when at least about 80%, 85%, 90%, 95% or 99% sequence identity polypeptides are found, then one skill in the art can make them. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to obtain "85%, 90%, 95% or 99%" nectin-3 polypeptide variants, to generate the infinite number of derivatives recited in the claims, and to determine the specific activity of the infinite variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Making and testing such polypeptides is clearly "well outside the realm of routine experimentation.

Applicant further argues that the Skolnick and Fetrow, Metzler et al., and Martinez et al. references for the proposition that the unpredictability of the art would render the skilled artisan unable to make and use the subject matter of the claims. However, as described above, even in the complete absence of any guidance as to which variants of amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ Nos. 4, 6, 10, 12, and 31 would be functional, the routine experimentation required to make and test such variants would not be so undue as to cause the claimed subject matter to be beyond the skill of the artisan. And as has been conceded by the Office Action at page 5, paragraph 4, Applicants have provided guidance for the production of functional variants.

Applicant is relying upon certain biological activities and the disclosure of three species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NOs: 4, 6, 10, 12, and 31 would have been altered such that the resultant polypeptide would have retained the function of inhibiting endothelial cell migration. Absent the ability to predict which of these polypeptides

would function as claimed for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Applicant asserts that the references the Office Action relies upon to support the assertion of unpredictability of the art, when read carefully in their entirety, actually demonstrate the fact that the skilled artisan can predict which variants are likely to be functional, especially in situations where guidance can be found from comparisons to related polypeptides. Applicant contends that the purpose of Skolnick and Fetrow, 2000. Trends in Biotech 18(1): 34-39 is to consider the assignment of biochemical function to proteins generally, based on amino acid sequence and/or on protein three-dimensional structure. Applicant contends that although the article does point out some limitations in using either sequence information alone or structural information alone (e.g. Box 2 of the article) to predict protein function, the authors also indicate that in many situations sequence-based approaches are successful in predicting function from structure. Applicant points to page 3, column 1 of the article, in the section entitled "Active-site identification", wherein Skolnick and Fetrow state that the approach of using amino acid sequence conservation as an indication of functionally important residues can be a valid one: "these results provide clear evidence that enzyme active sites are indeed more highly conserved than other parts of the protein". Further, Applicant contends that Box 2 of the article, relating to the use of three-dimensional protein structure alone to predict function, the authors state that "broad function-structure correlations were observed for some structural classes" of proteins. Also, in the section spanning pages 36 and 37, the authors describe successfully combining sequence and structural information to accurately identify proteins with disulfide-oxidoreductase activity, and they conclude at the bottom of the second column on page 37, "although **sequence-based approaches to protein-function prediction have proved to be very useful**, altematives are needed to assign the biochemical function of the 30-50% of proteins whose function cannot be assigned by any current method" (emphasis added by applicant). Applicant concluded that after a thorough reading of Skolnick and Fetrow, one would more fairly conclude that this reference teaches that sequence-based approaches to protein-function prediction can often, perhaps in most instances, be used successfully. It is difficult to apply the teachings of the Skolnick and application, because Scholnick and Fetrow reference directly to the nectin polypeptides of the present
Skolnick and Fetrow were assessing prediction of protein function either across all classes of protein structures or to particular types of enzymes, but when read in its entirely this reference certainly cannot be considered to teach an inability of the skilled artisan to predict the functionality of nectin-3 polypeptide variants from their amino acid sequence, especially when nectin-3 function (inhibiting endothelial cell migration) has already been experimentally established for polypeptides comprising nectin-3 amino acid sequences.

Contrary to Applicant assertions, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the

provide evidence that existing functional annotation methods is fraught with inaccuracies and that theses methods are still notably deficient in defining and describing the complexity of protein function. Therefore, even though the overall similarity of the structure of nectin-3 polypeptides with other nectin polypeptides: the three Ig domains, the transmembrane domain, and the similarity of sequences at the intracellular C-terminus that are seen in the members of the nectin polypeptide family only experimental research can confirm the artisan's best guess as the function of the structural related protein. Further, the claims encompass alterations in protein folding because claims do permit deviation from the amino acid sequences of the consensus regions for a non-native protein. It would be reasonable to conclude that alterations in protein folding would lead to a large alteration in binding affinity of nectin-3 with nectin-1.

Applicant states that the Examiner mischaracterizes the teaching of Metzler et al. Applicant submits that the Metzler et al dose not teach inconsequential chemical modification but rather the substitution of the Metzler et al were made in the amino acid residues that are either conservaed among CTLA4 species or homolgues or conserved among CTLA4 and CD28 species homologues. Applicant also submits that metzler et al teach the ability of the artisan to predict the function of polypeptide variants based on comparisons of amino acid sequences.

While the Examiner agrees with applicant that Metzler teaches substitutions in amino acid residues that are either conserved among CTLA4 species homologues or are conserved among both CTLA4 and CD28 species homolgues. However, the issue is still that single amino acid can determine the ligand specificity of the CTLA-4 and the unpredictable nature of amino acid alterations in the binding activity. Regarding Applicant conclusion that Metzler et al teach the ability of the artisan to predict the function of polypeptide variants based on comparisons of amino acid. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. The specification does not teach which changes in the amino acid of nectin-3 $\alpha$, $\beta$ or $\gamma$ would not alter all the activities of the polypeptide.

Applicant argues regarding Martinez et al., that the Examiner mistakenly concludes for the Martinez et al that " it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences". Applicant submits that Martinez et al teaches the ability of the skilled artisan to predict the functional importance of polypeptide residues based on amino acid sequence comparisons. Applicant states that it was expected by the authors that segments of the human nectin-2 V domain would confer HSV entry activity to mouse nectin-2, and conversely, that replacement of certain residues in the human nectin-2 V domain with residues from murine nectin-2, which has no HSV entry activity, would abolish the human nectin-2 HSV entry activity.

However, only experimental research can confirm the artisan's best guess as whether, the replacement of amino acid within region A and/or B would confer lack of activity in the human nectin-2. As noted by Martinez et al that studies are designed to determine how the variations in primary sequence influence the 3-D structure, interactation with various forms of alphaherpesvirus gD, and entry activity.

Applicant criticizes the Examiner for reciting Colbert V. Lofdahl as " it is unclear how this case supports the present enablement rejection. Applicant sees no relevance between the present rejection of claims and Colbert V. Lofdahl. The Examiner agrees with Applicant comments.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention with the different diseases as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

7. Claims 59-111 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed 10/3/03.

Applicant is in possession of a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189 to 250 and 287 to 342, and SEQ ID NO:13-16 wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration.

Applicant is not in possession of any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73; any substantially purified polypeptide comprising any amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amion acid identity across the length of amino acids 58-404 of SEQ ID NO:4 or 6 in clai 79, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or

99% amino acid identity across the length of amino acids 58 through 404 of SEQ ID NO: 4 or 6 in claim 80; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 86, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95%, or 99% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 87; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12 or 31 in claim 93, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12, or 31 in claim 94; any isolated polypeptide of claim 93 produced by a process comprising (a) culturing a recombinant host cell comprising any "polynucleotide" having nucleotide sequence encoding said polypeptide and (b) isolating said polypeptide in claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising a polynucleotide having a nucleotide sequence encoding said polypeptide or The polypeptide of claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising any polynucleotide having any nucleotide sequence encoding said polypeptide, wherein said nucleotide sequence is selected from the group consisting of nucleotide4s 172-1026 of SEQ ID NO:3, 5, 9 or 11; nucleotides 172-1212 of SEQ ID NO:3 or 5, and nucleotides 172-1098 of SEQ ID NO: 9 or 11 in claim 102; wherein said polypeptide comprises an amino acid sequence selected from the group consisting of (a) amino acids 58-342 of SEQ ID NO: 4, 6, 10, 12 or 31, (a) amino acids 58-404 of SEQ ID NO:4 or 6, (c) amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, (d) amino acids 74-404 of SEQ ID NO:4 or 6, (e) amino acids 58 through 365 of SEQ ID NO:10, 12, or 31 and (f) amino acids 74-365 of SEQ ID NO:10, 12 or 31 in claim 105, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell into which a polynucleotide comprising a nucleotide sequence encoding said polypeptide has been introduced in claim 111.

Applicant's arguments, filed 4/1/04, have been fully considered, but have not been found persuasive.

Applicant argue that they can find no clear basis for applying the rejection to claims 59-78, wherein the claims are directed to a polypeptide sequences that have been shown to possess the nectin-1 binding properties. Applicant further submits that the specification teaches show the structures of the nectin-3 extracellular domain are related to binding interactions with other molecules, and how these binding interactions are involved in biological processes such as endothelial cell migration. Applicant points to the specification the extracellular domain of nectin-3 polypeptides contains Ig domains, particularly the N-terminal V-type Ig domain, important for its ability to bind other nectins: "The N-terminal Ig domain of nectin-l and nectin-2 is a V-type Ig domain, while the two C-terminal Ig domains are C2-type domains. The N-terminal Ig domain of this family of molecules has been shown to be required for binding in

trans to other nectin molecules on adjacent cells in a hetero- or homotypic fashion." (Page 4, lines 6-9.) "Interaction of nectin polypeptides via their extracellular domains is involved in the movement or migration of epithelial and endothelial cells both in normal wound healing and in abnormal conditions such as restenosis." (Page 12, lines 26-28.) "Because the extracellular domain of nectin polypeptides binds to binding partners such as nectins and viral proteins, the extracellular domain, when expressed as a separate fragment from the rest of a nectin polypeptide, or as a soluble polypeptide fused, for example, to an immunoglobulin Fc domain, is expected to disrupt the binding of nectin polypeptides to their binding partners.

However, to satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563. The written-description requirement can be satisfied "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572. The specification does not identify variants and does not disclose a representative number of members. No variants were made or shown to have activity. Only the polypeptides of nectin-3 α, β and γ are disclosed. The specification's general discussion of making and identifying for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants or polypeptides comprising the specific amino acids. Putting the claimed polypeptide into practice awaited someone actually discovering a necessary component of the invention. Without the polypeptide variants or the polypeptide comprising the specific amino acids, Applicant could no more be said to have possessed the complete claimed invention.

Applicant's disclosure of additional sequences in the instant specification appear to be limited to fragments of the human nectin-3 amino acids and therefore do not provide additional insight into the identification of a representative number of species to provide written support for the broadly claimed genera.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
May 27, 2004

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